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Title: A large number of cutaneous neurofibromas beyond age-appropriate incidence in a patient with a large deletion of *NF1*.

Neurofibromatosis 1 (NF1) is an autosomal genetic disease caused by mutations of the *NF1* gene with a prevalence of approximately 1 in 3000 individuals.[1] Until now, only a few genotype-phenotype correlations in NF1 have been identified.[2] Although severity of NF1 are variable in degree, large *NF1* deletions have been reported to be accompanied by more severe clinical symptom.[3] We have already shown that the number of cutaneous neurofibromas significantly increases with age.[4] Herein we focus on the relationship between the number of cutaneous neurofibromas and the type of *NF1* mutation in consideration for each patient's age.

We studied 17 NF1 patients (4 men and 13 non-pregnant women; average age, 30.2 years; age range, 0-79 years) at the Dermatology Department of Tottori University Hospital from 2014 to 2016 after informed consent. All of the patients fulfilled the criteria for a diagnosis of NF1 by National Institutes of Health in 1988.[5] Blood samples were sent to Keio University for genetic analysis of *NF1*. Genomic DNA was extracted from peripheral blood according to standard procedures. In-solution hybridization-based enrichment was performed using the SureSelect Target Enrichment system (Agilent Technologies, Santa Clara, CA, USA). When the next-generation sequencing protocol

revealed truncating mutations, the variants were validated by direct capillary sequencing methods. The exon deletions were screened using a multiple ligation-dependent probe amplification method (SALSA P081/082-B2 NF1MLPA assay kit; MRC-Holland). We also counted the number of cutaneous neurofibromas (> 5 mm in diameter) excluding subcutaneous neurofibromas by visual judgment. Clinical severity of each patient was evaluated by DNB classification.[3] We investigated the relationship between the number of cutaneous neurofibromas and the type of mutations in detail. Ethics Committee of Tottori University Hospital approved the study protocol (No. G125).

As reported previously,[3] the number of cutaneous neurofibromas increased with age (Table 1). A patient No 13 (age, 47), in whom whole exon deletions were identified, had an extremely large number of neurofibromas beyond age-appropriate incidence (Fig. 1). She was accompanied by intellectual disability, hypertelorism and tall stature. Although small exon deletions were identified in patients 10 and 11, they showed age-appropriate number of neurofibromas. There was no evidence of association between each type of *NF1* mutation and DNB classification.

Large deletions of *NF1* occur in about 5% of the patients and are associated with severe manifestations.[2] It has been reported that patients with large *NF1* deletions exhibited a very high number of cutaneous and subcutaneous neurofibromas, and increased

frequencies of spinal neurofibromas and malignant peripheral nerve sheath tumors.[3] In addition, age is one of the most important factors in clinical manifestations of NF1. We have to keep in mind the influence of increasing age on the development of cutaneous neurofibromas. In this study, we found that a large number of cutaneous neurofibromas develop in a patient with a large *NF1* deletion beyond age-appropriate incidence, which would be a clue for the diagnosis of severe phenotype of NF1.